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Neither dosage nor serum levels of antiepileptic drugs are predictive for efficacy and adverse effects

• M.W. Lammers, Y.A. Hekster, A. Keyser, H. van Lier, H. Meinardi and W.O. Renier

Introduction

The purpose of this study is to demonstrate the use of two measures for therapeutic potency when assessing antiepileptic therapy, in particular when using multiple drugs (polypharmacy). Furthermore, we investigated the correlation between pharmacotherapy and quantitative outcome measures using an adaptation of scales developed for drug trials by the Veteran Affairs Cooperative Study Group [1]. In particular, we were interested whether either drug dosage or serum levels would be the best indicators for outcome of treatment.

In the 1960s and 1970s, measurement of serum levels of antiepileptic drugs (AEDs) was increasingly used for monitoring antiepileptic pharmacotherapy. Notwithstanding the publication of several monographs devoted to this topic, it is still controversial whether a clear-cut relationship exists between serum level and efficacy or serum level and side-effects. In particular in polypharmacy, where metabolic interactions may occur, it is important to know how serum levels are to be interpreted.

For the measurement of exposure to AEDs in the case of polypharmacy, we used the prescribed daily dose/defined daily dose (PDD/DDD) ratio, as described in previous papers [2-4]. In analogy with the PDD/DDD ratio, we propose the use of the observed serum level/average therapeutic level (OSL/ATL) ratio as a tool for the study of AED efficacy. In order to determine the nominator of this ratio, we used the therapeutic ranges as published in handbooks and other publications.

To assess whether this OSL/ATL ratio can be used as a parameter to predict drug effects, we studied the data of a population of epileptic patients on monopharmacy and polypharmacy. We also used indices to obtain quantitative outcome measures for the efficacy and for adverse effects of the treatment. These indices, which are summarized by the composite index of impairments (CII), are briefly explained in the *Methods* section.

For 100 patients on monopharmacy and 100 on polypharmacy we assessed whether the PDD/DDD ratio or the OSL/ATL ratio was the better predictor of the CII. The prediction of each of the subindices was assessed separately. The correlation between the OSL/ATL ratios and the PDD/DDD ratios was also examined.

Methods

Population

Patients who were referred to tertiary epilepsy care facilities in the Netherlands were studied. The population sampled consisted of out-patients from the Instituut voor Epilepsiebestrijding in Heemstede, from one of the Institute's regional out-patient departments in Utrecht, and from the Hans Berger Kliniek in Breda. A previous study established that

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Epilepsy
Serum concentration

Abstract

In order to assess whether doses or serum levels are predictive for the efficacy and adverse effects of antiepileptic drugs (AEDs), measures for exposure to drug combinations have to be used. For doses, the ratio of the observed prescribed daily dose (PDD) and the average defined daily dose (DDD) considered effective for the main indication of the drug was used. In analogy for serum levels, the OSL/ATL ratio, *i.e.* the ratio of the observed serum level and the average therapeutic level was used. In polypharmacy these ratios can be summed as they are normalized measures of strength. The correlations of these ratios with outcome measures were studied in 200 patients attending out-patient clinics of special centres for epilepsy; half of these patients were treated with monopharmacy and half with polypharmacy. As outcome measures the following indices were used: the index of seizures, which quantifies seizure type and frequency, the seizure activity index, the neurotoxicity score, the systemic toxicity score, and the composite index of impairments, which is the sum of the seizure activity index and the neurotoxicity score and the systemic toxicity score. When all data were pooled, the correlation coefficient between the PDD/DDD ratio and the OSL/ATL ratio was 0.77. However, when the data were examined separately for the monopharmacy and polypharmacy groups, the correlation was 0.31 for the monopharmacy group and 0.50 for the polypharmacy group. Neither the PDD/DDD ratio nor the OSL/ATL ratio correlated with the composite index of impairments or with any of the individual indices. Factors such as the difficulty of titrating the endpoint of seizure suppression and the development of tolerance to adverse drug effects may perhaps be responsible for these findings. This observational study signals the problem.

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there are no differences in patient characteristics or treatment approach between these three locations [3]. These patients cover a wide range: at one end patients are well controlled by AEDs but are under treatment for psychosocial problems; at the other end patients are resistant to present-day AEDs. Therefore this cohort is particularly suited for comparative studies on correlations of therapy and outcome.

If the patients met the selection criteria, they were asked to participate in the study, which was linked with their regular visit to their attending physician. For the present study the data of the first 100 patients who were treated with monopharmacy and the first 100 patients who were treated with polypharmacy were examined. Of these 200 patients, 60 patients visited their attending physician twice within the time span of the intake period, and on both occasions blood samples were taken. The data from patients who had a change in drug dosage ($n = 35$) were analysed separately to determine whether or not a correlation existed in individual patients between either the PDD/DDD ratio or the OSL/ATL ratio and the clinimetric indices. The study was approved by the Ethics Committees of both Institutes.

Selection criteria

Patients who visited an adult out-patient epilepsy clinic were included. These patients suffered from well-defined types of seizures according to the International Classification of the International League Against Epilepsy.

Patients with factors that were believed to complicate the evaluation process, such as progressive brain disorders, obvious non-compliance with drug usage or seizure registration, pseudo-seizures and severe mental retardation, were excluded from the study. Patients who were treated with vigabatrin were also excluded as the mechanism of action of this drug is typically independent of steady-state serum levels.

Analysis of drug treatment and dosage

In order to compare the effect of one drug with the effect of a combination of several other drugs, it is necessary to find a measure of equipotency. To this end, all daily dosages were standardized using the PDD/DDD ratio. The PDD is the dose prescribed by the physician for the individual patient, and as only compliant patients were admitted to the study, the PDD equals the observed daily dose. The DDD is the assumed average effective dose per day for the drug used in its main indication in adults. The DDD is expressed in terms of the amount of the active substance. DDD values are assigned by the WHO Collaborating Centre for Drugs Statistics Methodology and the Nordic Council on Medicines, which regularly publish "Guidelines for Defined Daily Doses". This publication is based on dose-documents per drug as prepared by WHO Oslo, based on international textbooks, journals and documentation approved by drug control authorities. The dose-documentations are available on request from the WHO Collaborating Centre, Oslo [5]. The published DDDs of AEDs are presented in Table 1.

The rationale of adding up the PDD/DDD ratios of different AEDs is based upon the definition of DDD

Table 1 Defined daily dose (DDD) and average therapeutic level (ATL) per antiepileptic drug

Antiepileptic drug	DDD (mg) [5]	ATL ($\mu\text{g/ml}$) [6-12]
Carbamazepine	1000	7
Clobazam	20	0.35
Clonazepam	8	0.04
Ethosuximide	1250	70
Oxcarbazepine	1000	22
Phenobarbital	100	30
Phenytoin	300	15
Valproate	1500	70

as the maintenance dose of that particular drug for the main indication in adults. According to the WHO Defined Daily Dose Model, half a DDD of AED-I plus half a DDD of AED-II should be as effective as a full dose of either of them. For example, 750 mg valproate plus 500 mg carbamazepine should be as effective as 1500 mg of valproate or as 1000 mg of carbamazepine. For combinations it may ultimately appear that the PDD/DDD ratio for a particular combination, which is the "average effective dose per day for the drug-combination used in its main indication in adults" may be less than unity (supra-additive effect) or greater than unity (infra-additive effect). However, we are not concerned with efficacy itself, but with comparison of the PDD/DDD ratio and the OSL/ATL ratio as a parameter for therapeutic potency.

Analysis of serum levels

In analogy to the ratio for drug dosage, we constructed a ratio for the serum levels of the AEDs, the OSL/ATL ratio. The ATL (average therapeutic level) was assessed by averaging data from papers published on this issue [6-12]. These papers often present a therapeutic range. We used the serum levels of seizure-free patients on monotherapy. If a range was published, the average of the minimum and maximum value was taken. We assume that, given the present AEDs, patients seizure-free on drug A at an average therapeutic serum level should also be well controlled by drug B when its average therapeutic serum level is reached. The ATL for each drug used in this study is shown in Table 1. The OSL (observed serum level) is the serum level found for each AED prescribed to the patient. As was done for the PDD/DDD ratio, the OSL/ATL ratios were summed when the patients were treated with polypharmacy.

Analysis of treatment outcome

For the analysis of treatment outcome, we used the index of seizures, the seizure activity index, the neurotoxicity score, and the systemic toxicity score, which are combined to form the composite index of impairments (CII). The CII is derived from the composite index used in the Veterans Affairs study of the efficacy and toxicity of AEDs [1] and has been validated in a study by Wijsman *et al.* [13].

The index of seizures is a rating scale which considers seizure frequency as well as seizure type. The index may be modified by factors which are con-

sidered to influence seizure severity, such as the presence of an aura, avoidable provocative factors, seizures during sleep only, clustering of seizures, and the duration of impairment after the seizure. This modified index of seizures results in the seizure activity index. We used a neurotoxicity score and a systemic toxicity score to quantify the toxicity of a medication. The score ranges are graded according to the severity of the toxicity.

The CII denotes the total of the impairments due to the disorder, as it considers both the seizure activity index, the neurotoxicity score and the systemic toxicity score, which are summed. The outcome of treatment, as reflected by the CII score, was classified into four groups [13]:

- 1 CII = 0: optimal epilepsy control;
- 2 CII = 1-10: acceptable but suboptimal epilepsy control;
- 3 CII = 11-49: fair-to-poor but not an unacceptable epilepsy control;
- 4 CII ≥ 50: unacceptable epilepsy control.

Blood sampling

After we obtained the patient’s consent, blood samples were taken for monitoring clinical chemistry, such as electrolytes, liver and kidney function, haematological evaluation of toxicity (idiosyncratic reactions, allergies), and therapeutic drug monitoring, *i.e.* to measure drug concentration in steady-state conditions, to identify individual pharmacokinetics, to anticipate individual variations in drug utilization and drug–drug interactions, and to identify non-compliance.

Blood sampling was omitted if data for previous blood samples were available and representative for the patient’s current clinical state, provided no treatment changes or other destabilizing events occurred during the interval and provided the interval did not exceed 12 months. Measurements were performed by routine methods for therapeutic drug monitoring (high-pressure liquid chromatography) [12]. When blood sampling was repeated, blood sampling for each individual patient was always at the same time of the day.

Patient data collection

After the visit to the clinician, the patients were interviewed and examined by the investigator in order to

obtain data necessary for the determination of the indices without prior knowledge of the treatment dose or serum levels. Subsequently, the patient’s file was handed to the investigator in order to complete the research file. Patient seizure charts of past year(s) were studied in order to determine fluctuations in seizure frequency since the last treatment change. The medication and doses prescribed as well as the corresponding serum levels were noted. This allowed for the assessment of the PDD/DDD ratio and the OSL/ATL ratio per individual drug.

Statistical analysis

The χ^2 test was used to analyse possible differences in population characteristics of the group on monopharmacy and polypharmacy. Spearman’s correlation coefficient was used to analyse correlations. A correlation was considered good when the correlation coefficient was at least 0.70.

Results

Population characteristics

103 men and 97 women participated in the study. The mean age was 39. The age of seizure onset did not differ significantly between patients on monopharmacy and patients on polypharmacy, although more patients on polypharmacy had had seizures since infancy. 151 patients had partial seizures and 49 generalized seizures. In the group treated with monopharmacy more patients had generalized seizures than in the group treated with polypharmacy, 29 and 20, respectively.

Treatment

Carbamazepine was prescribed most frequently for patients on monopharmacy, *i.e.* for 48 patients, followed by valproate (35 patients). The other AEDs used in monopharmacy were phenytoin (9 patients), oxcarbazepine (5 patients), and phenobarbital (3 patients). Carbamazepine was also the most frequently prescribed AED for patients on polypharmacy, *i.e.* for 86 patients, followed by valproate (55 patients). For patients on polypharmacy, the mean number of AED per patient was 2.5: 60 patients were prescribed 2 AEDs, 38 patients 3 AEDs, and 2 patients 4 AEDs.

Table 2 Median prescribed daily dose/defined daily dose (PDD/DDD) ratios for individual antiepileptic drugs

Drug	Monopharmacy		Polypharmacy	
	median PDD/DDD ratio (range)	n	median PDD/DDD ratio (range)	n
Carbamazepine	0.7 (0.1-2.0)	48	0.9 (0.2-2.0)	86
Clobazam	–	–	0.7 (0.5-2.0)	13
Clonazepam	–	–	0.13 (0.13)	5
Ethosuximide	–	–	0.6 (0.2-1.2)	12
Oxcarbazepine	0.6 (0.4-0.9)	5	1.3 (0.6-2.0)	2
Phenobarbital	0.8 (0.5-1.0)	3	0.7 (0.1-2.1)	21
Phenytoin	1.1 (0.6-1.3)	9	1.1 (0.5-2.0)	47
Valproate	0.8 (0.2-1.3)	35	1.0 (0.4-2.3)	55

Table 3 Median observed serum level/average therapeutic level (OSL/ATL) ratios for individual antiepileptic drugs

Drug	Monopharmacy		Polypharmacy	
	median OSL/ATL ratio (range)	n	median OSL/ATL ratio (range)	n
Carbamazepine	0.92 (0.24-1.44)	48	0.89 (0.29-1.67)	86
Clobazam	—	—	1.08 (0.23-2.71)	13
Clonazepam	—	—	1.44 (0.43-2.50)	5
Ethosuximide	—	—	0.63 (0.21-1.37)	12
Oxcarbazepine	0.54 (0.30-0.85)	5	0.17 (0.13-0.20)	2
Phenobarbital	0.59 (0.17-0.99)	3	0.56 (0.04-1.21)	21
Phenytoin	0.79 (0.19-1.49)	9	0.88 (0.31-1.67)	47
Valproate	0.97 (0.50-1.76)	35	0.89 (0.23-1.71)	55

Prescribed daily dose/defined daily dose ratio

For all drugs used in the group of patients on monopharmacy, the median PDD/DDD ratio was 0.7 (range 0.1-2.0; Table 2) and the mean PDD/DDD ratio was 0.8. In the group on polypharmacy, the median sum of all PDD/DDD ratios per prescription was 2.1 (range 0.7-5.2). The mean of these summed PDD/DDD ratios was 2.2. In the polypharmacy group, the median PDD/DDD ratio for the individual AED in the composite prescriptions was higher than the median PDD/DDD ratio of these drugs when prescribed alone, with the exception of phenobarbital (Table 2).

Observed serum level/average therapeutic level ratio

The median OSL/ATL ratio for the patients on monopharmacy was 0.90 (range 0.17-1.76), as was the mean OSL/ATL ratio, and for the patients on polypharmacy the median of the sums of OSL/ATL ratios of the component drugs was 2.00 (range 0.83-4.50), with a mean sum of OSL/ATL ratios of 2.10.

The median OSL/ATL ratio for the individual AED measured in the serum of patients on polypharmacy was lower than the median OSL/ATL ratio for the same drug when the patients were treated with monopharmacy, with the exception of phenytoin (Table 3). The median PDD/DDD ratio per drug increased when the number of drugs per patient increased; however, the OSL/ATL ratio per drug decreased.

Correlation between study parameters

There was a good correlation between the PDD/DDD ratio and the OSL/ATL ratio if all patients were considered (correlation coefficient 0.77). The correlation decreased when this correlation was tested separately for the polypharmacy and the monopharmacy

groups. The correlation between these two ratios was better for the patient group on polypharmacy than for the patient group on monopharmacy (correlation coefficients of 0.50 and 0.31, respectively).

When looking at the whole population (n = 200), for the PDD/DDD ratio as well as for the OSL/ATL ratio, the correlation with the clinimetric indices was marginal, although it was slightly better for the PDD/DDD ratio than for the OSL/ATL ratio, but this difference was not significant (p > 0.05) (Table 4). For the group on polypharmacy, the correlations of both ratios with the clinimetric indices were slightly better than for the group on monopharmacy, but again this difference did not reach statistical significance (p > 0.05) (Table 4).

There was no correlation between the two ratios at different times and doses, and the corresponding clinimetric indices of the 35 patients who had had a change of dosage during the observation period and who were assessed individually.

Discussion

The use of polypharmacy makes it difficult to compare the strength of the medications prescribed to a patient at different times or between patients. The ratio of the prescribed daily dose to the defined daily dose is an internationally recognized tool to make such comparisons possible. The WHO Collaborating Centre for Drugs Statistics Methodology and the Nordic Council on Medicines in Oslo regularly assess and publish the defined daily doses. In monopharmacy, the serum level of the administered drug is assumed to provide a better indication of the active amount of drug aimed at the target than the dose itself. In polypharmacy, this relationship has never been studied. We proposed to use the ratio of the observed serum level over the average 'therapeutic'

Table 4 Correlation coefficients of the prescribed daily dose/defined daily dose (PDD/DDD) ratios and the observed serum level/average therapeutic level (OSL/ATL) ratios with the clinimetric indices

Clinimetric index	Overall		Monopharmacy		Polypharmacy*	
	PDD/DDD	OSL/ATL	PDD/DDD	OSL/ATL	PDD/DDD	OSL/ATL
Index of seizure	0.24†	0.23†	0.26†	0.15‡	0.15‡	0.22†
Seizure activity index	0.21†	0.20†	0.26†	0.18‡	0.16‡	0.20†
Neurotoxicity score	0.40†	0.34†	- 0.07‡	0.06‡	0.27†	0.15‡
Systemic toxicity score	0.01‡	- 0.01‡	- 0.03‡	- 0.15‡	- 0.18‡	- 0.16‡
Composite index of impairments	0.31†	0.28†	0.13‡	0.07‡	0.18‡	0.17‡

* Summed ratios per prescription.

† $p < 0.05$.

‡ $p > 0.05$.

level (OSL/ATL) as parameter. This parameter is a normalized measure of the strength of the levels found and these can therefore be summed as long as they concern drugs given for the same purpose. It might be argued that polypharmacy should be avoided and that it is an academic exercise to study polypharmacy. Indeed, while Guelen *et al.* still report an average use of 3.2 AEDs per patient [14], we found an average number of AEDs prescribed per patient of 1.7. This reflects a tendency to prefer monopharmacy over polypharmacy. However, polypharmacy is certainly not being phased out, because as recently as the 20th International Epilepsy Congress, which was held in July 1993 in Oslo, a satellite symposium was devoted to rational polypharmacy in the treatment of epilepsy.

In our study the median PDD/DDD ratio per drug was lower for patients on monopharmacy (0.8) than the median sum of PDD/DDD ratios for patients on polypharmacy (2.2). Comparison of the median PDD/DDD ratio in monopharmacy and the median PDD/DDD ratio for the same individual drugs applied in composite prescriptions (polypharmacy) showed that this value was always slightly higher in polypharmacy, notwithstanding the fact that in many cases several drugs were used simultaneously (Table 2). The only exception was phenobarbital.

In polypharmacy, the PDD/DDD ratios for the individual drugs were close to unity. The median PDD/DDD ratios for clonazepam and ethosuximide were, however, appreciably lower than unity. It is possible that the daily dosages advised by the WHO Collaborating Centre for Drug Statistics for these AEDs are too high. This is quite likely in the case of clonazepam, as the median OSL/ATL ratio was high (1.44). However, this is not the case for ethosuximide, which had very similar median PDD/DDD and median OSL/ATL ratios (0.57 and 0.63). While in

polypharmacy the median PDD/DDD ratio of an individual drug increased, the median OSL/ATL ratio of an individual drugs decreased, reflecting metabolic interaction.

The correlation of the PDD/DDD ratio with the outcome measures for seizures and toxicity were both poor. Better correlations were seen between the PDD/DDD ratio with the clinimetric indices and between the OSL/ATL ratio with the clinimetric indices with polypharmacy than with monopharmacy. However, the difference was not statistically significant. The lack of correlation meant that we could not study possible supra-additive or infra-additive effects of polypharmacy. Even when two sets of data per patient were available, no statistical significance was found when we assessed the correlation within patients between the PDD/DDD ratio, the OSL/ATL ratio and the clinimetric indices.

The results of this study support the assertion that a difference in dosage or serum levels of AEDs does not predict a difference in either efficacy or adverse effects of these drugs. The reasons can only be guessed at. As far as the OSL/ATL is concerned, there may be a biochemical reason as not all metabolites have yet been identified and nothing is known about their intrinsic activity on efficacy and adverse effects. For this reason it was also not possible to incorporate an OSL/ATL ratio for known metabolites in our equation. Another plausible reason for the disappointing results is that the paroxysmal character of the seizures makes it difficult to accurately titrate the endpoint 'freedom from seizures'. The dose may well have been higher than necessary in those patients who were seizure-free.

With respect to the outcome measures of drug toxicity, the occurrence of tolerance to adverse effects may interfere with the expected relation between the PDD/DDD or OSL/ATL and the neuro-

toxicity score and the systemic toxicity score. As this was an observational study, the material does not permit an answer to these questions, it can only signal the problem.

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